The Importance of Adverse Event Reporting

BY ARON SHAPIRO

Clinical trials are all about the participants. Those who voluntarily participate in retina trials are putting their faith and trust in the sponsor, the clinical investigator, and the trial personnel to safeguard their health and well being. With each clinical trial, these participants help increase knowledge, guide medical decisions, and benefit patients—the ultimate end consumer of approved medications—and the medical system. Participant safety reporting systems are a critical part of the process as they help catalogue drug-associated events throughout the clinical trial process and after a product has been approved through postmarketing surveillance.

THE IMPORTANCE OF REPORTING

Reporting is fundamental to detecting subject safety issues. Each clinical trial protocol should clearly state the method(s) by which adverse events will be monitored and reported. Provisions to ensure proper care for those experiencing unfavorable and unintended signs or symptoms associated with their participation in a clinical trial are a necessary component as well. The protocol should also describe how information relating to adverse events is to be handled and analyzed by the investigator and sponsor, and their responsibilities to inform each other, governing institutional review boards (IRBs), and the US Food and Drug Administration (FDA).

The rise in multicenter studies has complicated the reporting pathways for adverse events.[1] A high number of individual, unanalyzed events from a number of sites within the same study hinders the ability of the FDA to ensure the protection of human participants. Incomplete safety reports also limit understanding adverse events in the context of the entire study, rather than at just 1 site. Each investigator relies on the sponsor to provide timely updates and provide details about study drug-related adverse events occurring at other sites so they can make informed medical decisions. Therefore, accurate, complete, and on-time reporting of these events from the investigator to the sponsor is essential to the sponsor's effective evaluation and management of the study's safety data. The sponsor is responsible for informing the FDA according to specific timelines. The sponsor, the IRB, and the FDA all use safety information to make critical decisions that have a significant impact on the clinical trial, all intended to protect human participants.

SAFETY DATABASE AND DATA MONITORING COMMITTEE

To manage safety reports coming in from multiple study centers across multiple studies, a safety database is often used. Because it is difficult to consider the implications of a single adverse event independent of the study, a repository of all adverse events for a single drug can help to elicit and flag potential trends. In order to make use of the safety database to monitor trial data and participant safety as a study is ongoing, however, sponsors may establish an independent data-safety monitoring committee. The committee is composed of a group of experts independent of the study from all scientific disciplines, including clinical trial experts, biostatisticians, and clinicians who are knowledgeable about the disease as well as the drug's mechanism of action. This group is tasked with monitoring subject safety and treatment efficacy data while clinical trials are being conducted. For example, if adverse events of a particularly serious nature are more common in the experimental arm compared with the control arm, the committee would then need to consider the risk/benefit of the study and whether it is safe to continue. Typically, the data and safety monitoring committee will first meet in an open session, during which the sponsor and/or those involved in running the clinical trial may participate to discuss data in a masked fashion. Following this open session, a closed session consisting of only the independent board members will review emerging trial data. A study's medical monitor will also work closely with the safety committee to

provide oversight and evaluate information relevant to the safety of the product.

RECORDING ADVERSE EVENTS

It is important to keep in mind that large volumes of individual adverse event reports that lack context and detail or that do not satisfy reporting thresholds inhibit the FDA from efficiently evaluating safety information. Ultimately, this detrimentally affects the safety process rather than enhancing the FDA's ability to protect human participants. When recording an adverse event, investigators should consider the following: severity, study intervention relationship, the action taken regarding the study intervention, the outcome of the adverse event, whether it was expected or unexpected, and whether it was serious. In the case of severity, the investigator might use the adjectives mild, moderate, or severe to describe the maximum intensity of the adverse event. The definitions of the intensity grade should be defined within the protocol. For example, mild may be defined as "does not interfere with a participant's usual function"; moderate as "interferes to some extent with participant's usual function"; and severe as "interferes significant;y with participant's usual function." It is important to also consider the distinction between the gravity and the intensity of an adverse event. Severity is a measure of intensity: thus, a severe reaction is not necessarily a serious reaction. The investigator should also note whether the adverse event is serious or nonserious, and the relationship of the event to study drug (ie, not related, possibly related, definitely related). In addition to seriousness, these criteria help the sponsor to determine if the event should be reported to the FDA. This classification of gravity of the event determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting to the IRB and regulatory agency should follow local and international regulations, as appropriate.

The investigator in any clinical trial must document in the participant's study records all directly observed adverse events and all adverse events spontaneously reported by the study participant. Additionally, each study participant should be questioned about adverse events at each visit. All of these adverse events, regardless of their severity, become part of the safety database for the drug or device under investigation.

WHAT AND WHEN TO REPORT?

In order to comply with the requirements for Investigational New Drug (IND) safety reporting, sponsors are required to notify the FDA and all participating investigators of any suspected adverse reaction to a study treatment that is both serious and unexpected.[2] Should the event not meet all 3 components (be a suspected adverse reaction, serious, and unexpected), it should not be submitted as an IND safety report. The FDA has stated that review of these criteria should be guidance on whether a suspected adverse reaction should be reported to it.[2] Sponsors who have determined that a suspected adverse reaction qualifies for reporting have 15 days to submit an IND safety report to the FDA. Unexpected fatal or life-threatening suspected adverse reactions are considered a high priority, and a report should be submitted no later than 7 days after receiving the information. Investigators are also required to report to IRBs any unanticipated problems involving risk to human participants, which includes, but is not limited to, serious and unexpected adverse events.

A suspected adverse reaction is different from an adverse event. For the purposes of IND safety reporting, the former is an adverse event for which there is a "reasonable possibility that the drug caused the adverse event," whereas the latter is any "untoward medical occurrence associated with the use of the drug" without any implication of causality.[2] To clarify a phrase that has brought about some confusion in regard to reporting standards, "reasonable possibility" is defined as "there is evidence to suggest a casual relationship between the drug and the adverse event."[2] An event or suspected adverse reaction is unexpected if it is not listed in the investigator brochure as a possible occurrence. An event is usually classified as serious if it resulted in death, is life-threatening, or caused hospitalization.

Generally speaking, the most difficult determination is deciding whether the adverse event is indeed a suspected adverse reaction. It is up to the sponsor to evaluate the information at hand to determine if there is a reasonable possibility that the drug caused the event, thus making it a suspected adverse reaction.[2] Certain adverse events are informative as single cases because they are known to be associated with drug exposure and should be reported; however, if a single event occurs and it cannot be determined that there is a reasonable possibility that the drug caused the event, then it is not a suspected adverse reaction.

POSTMARKETING SURVEILLANCE AND POLICIES

As part of the FDA Amendments Act of 2007, a new law to enhance drug safety, the FDA can require a Risk Evaluation and Mitigation Strategy (REMS) to manage a known or potential serious risk associated with a drug. Examples of these safety strategies include Medication Guides, Patient Package Inserts, communication plans, and other elements to assure safe use by patients. REMS

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may be required as part of the approval of a new product or when new safety information arises for products that have already been approved.

Premarketing clinical trials can last several years and involve hundreds of participants and, if successful, land a drug on the market. While great lengths are taken to ensure participant safety throughout each clinical trial phase, these premarketing trials cannot always ensure the complete safety of a new drug or evaluate all adverse events. A more realistic vision of a product's safety emerges after it has been introduced into the market. The FDA's Adverse Event Reporting System (FAERS), MedWatch, was founded in 1993 by David A. Kessler, MD. Kessler, the FDA's commissioner at the time, founded MedWatch with the hopes that it would facilitate the process of reporting serious adverse events. Although reporting of adverse events by health care professionals and consumers is voluntary in the United States, manufacturers that receive adverse event reports are required to forward these reports to the FDA. Patients and consumers are encouraged to fill out a report; however, a more detailed account may require the assistance of a health care professional. Spontaneous reporting continues to play a vital role in ensuring the effectiveness of MedWatch. The more information generated about specific drugs and devices, the more safe and effective the products can be for the individuals using them. Because the FDA most likely could not handle the influx of information regarding every adverse event, MedWatch is intended for the reporting of serious adverse events. Over-reporting is just as harmful as under-reporting, as it clutters a system designed to pinpoint critical information.

CONCLUSION

Although each adverse event is unique, there are likely to be similarities and patterns in sources of risk, which may otherwise go unnoticed if incidents are not reported and analyzed. It is important to understand each adverse event not as an isolated event but in conjunction with other reported events to consider the relevance and significance of those events to the study drug and the study. Both the act of reporting and the action taken in response to reporting leads to improved participant safety. ■

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1. Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126572.pdf. Accessed August 28, 2013.
2. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf. Accessed August 29, 2013.